Medical and Pediatric Oncology 28:179–182 (1997)

Prognostic Significance of Chemotherapy Dosage Characteristics in Children With Osteogenic Sarcoma

Sylvie Leung, MB, BS,[1] Glenn M. Marshall, MD,[1,4]* Mohammed Al Mahr, MB, BS,[1] Vivienne Tobias, MB, BS,[2] Doris B.G. Lee, BSc,[3] and Darcy O'Gorman Hughes, MD[1,4]

High-dose methotrexate (HDMTX), adriamycin (ADR), and cisplatinum (CDDP) are effective agents in the treatment of osteogenic sarcoma (OS). Individual patient doses are determined by prior successful clinical trials but may be reduced due to ongoing toxicities. It is unknown whether individualized dose reductions of these drugs influence disease outcome. We retrospectively studied 27 consecutively enrolled children treated with HDMTX, ADR, and CDDP as adjuvant chemotherapy for OS, for correlations between disease outcome and several characteristics of drug dosing: the cumulative MTX, CDDP, and ADR doses administered and the mean MTX blood levels for each patient. With a median follow-up of 59 months, the actuarial overall and disease-free survival rates were 70% and 59%, respectively. Factors which favorably influenced prognosis on univariate analysis were a cumulative ADR dose of >300 mg/m^2 ($P = 0.0002$) and a cumulative MTX dose >114 gm/m^2 ($P = 0.0048$). By multivariate analysis only the cumulative ADR dose >300 mg/m^2 retained prognostic value. We conclude that adjuvant chemotherapy dosages may need to be adjusted for therapeutic efficacy in addition to adjustments made for toxicity. The effect of different cumulative HDMTX and ADR dosages on prognosis in osteosarcoma patients needs to be evaluated in a prospective trial. **Med. Pediatr. Oncol. 28:179–182**

Key words: osteosarcoma; methotrexate; adriamycin; cisplatinum; prognosis

INTRODUCTION

With the use of adjuvant chemotherapy and operative removal of the primary tumor the 5-year survival rate for patients with osteogenic sarcoma (OS) is now 50–70% [1–3]. High-dose methotrexate (HDMTX) with citrovorum rescue (CFR) and adriamycin (ADR) were first noted to favorably improve the prognosis of metastatic OS in the early 1970s as single agents [4–6]. Cisplatinum (CDDP) also demonstrated promise in the late 1970s [7]. During the next decade DMTX, ADR, and CDDP were trialled in various combinations for patients with OS [8–10], and now these three agents form the basis of adjuvant treatment protocols for primary OS [3,11,12].

The two most important prognostic factors in patients with OS have been the amount of tumor necrosis at delayed primary resection following preoperative chemotherapy and the presence of metastases at diagnosis [3,11,13,14]. A high degree of primary tumor necrosis, in response to initial chemotherapy, is a good prognostic factor regardless of the cytotoxic agents used. More recent studies have suggested that drug resistance factors such as the P-glycoprotein level in the primary tumor tissue may explain the resistance of some tumors to chemotherapy [15]. However, still other patient- and tumor-specific factors may exist to explain chemoresistance in some patients.

While chemotherapy doses of HDMTX, ADR, and CDDP were calculated on the basis of patient surface area, dose reductions were often made during the course of therapy due to individual patient toxicities of hematologic, renal, hepatic, cardiac, or nervous systems in as many as 80% of patients receiving these agents [16]. MTX blood levels were determined following each course of HDMTX so that fluid and CFR regimens could be adjusted to avoid severe mucositis and hepatic, renal, and nervous system damage. Differences between individual patient renal and hepatic functions may explain the variation in the incidence of side effects requiring dose reductions. It is hoped that dose reductions, made to avoid excessive treatment side effects in non-malignant tissues, do not reduce the effectiveness of the chemotherapy regimen against malignant cells. In this retrospective study we investigated whether the variance in dosing characteristics for HDMTX, ADR, and CDDP in patients with OS predicted for prognosis.

[1]Department of Haematology and Oncology, Sydney Children's Hospital; [2]Departments of Anatomical Pathology and [3]Clinical Chemistry, Prince of Wales Hospital, [4]School of Paediatrics, Faculty of Medicine, University of New South Wales, Kensington, Sydney, Australia.

*Correspondence to: Dr. Glenn M. Marshall, Department of Haematology and Oncology, Sydney Children's Hospital, High Street, Randwick, 2031, Sydney, N.S.W., Australia.

Received 29 January 1996; accepted 10 May 1996.

TABLE I. Drug Dose Characteristics

Drug	Mean cumulative dose/m^2 (S.E.M.)	Disease-free survival	
		χ^2	P
MTX	114 (46) g	7.967	0.005
ADR	303 (24) mg	12.583	0.004
CDDP	354 (46) mg	0.003	0.953

MATERIALS AND METHODS

Twenty-seven patients consecutively diagnosed with OS between 1981 and 1992, treated at the Sydney Children's Hospital, Sydney, Australia, were retrospectively studied for the details of actual cumulative chemotherapy doses of HDMTX, CDDP, and ADR given and the mean serum MTX levels achieved at 4 (peak), 24, and 48 hr after commencement of the HDMTX infusion.

All patients received adjuvant chemotherapy for 2–3 months, followed by delayed primary tumor resection, and then further chemotherapy for 4–6 months. All 27 patients received HDMTX (12 g/m^2/course), ADR (75 mg/m^2/course), and CDDP (100 mg/m^2/course). The HDMTX was given on consecutive weeks, each 4 weeks to a total of 12 courses, while ADR and CDDP were administered each 4–5 weeks to a total of 5 and 4 courses, respectively. The intended cumulative doses for all patients were the same: HDMTX (12 g/m^2/course $\times$ 12) = 144 g; ADR (75 mg/m^2/course $\times$ 5) = 375 mg; CDDP (100 mg/m^2/course $\times$ 4) = 400 mg. In addition to HDMTX, ADR, and CDDP, 4 patients received vincristine (1.5 mg/m^2) with each course of HDMTX, and 3 of these 4 patients received 4 courses of BCD [bleomycin (15 mg/m^2), cyclophosphamide (600 mg/m^2), and actinomycin D (0.6 mg/m^2)]. Two patients did not receive CDDP due to preexisting renal dysfunction. All drug doses were calculated per square meter for the surface area at the time of each course, and then a mean was derived for each patient for the total duration of therapy. Leucovorin rescue was administered orally or intravenously every 6 hr at a dose of 15 mg/m^2 from 24 hr after the start of the MTX infusion for a total of 10 doses. After amputation, drug doses were reduced by the proportion of surface area contributed to by the amputated limb.

HDMTX, ADR, or CDDP doses for individual courses were reduced by 10 to 20% for World Health Organization grade 3 or 4 toxicities, respectively. The reduced dose was then given in all subsequent courses. Severe toxicities requiring dose reductions were mucositis, persistent hepatotoxicity or nephrotoxicity due to HDMTX, ototoxicity or nephrotoxicity due to CDDP, and myelosuppression and mucositis due to ADR.

All patients had their serum MTX levels (μmol/l) determined by the fluorescence polarization immunoassay method [17,18]. All 27 patients were analyzed for the prognostic effect of serum MTX, while the 2 patients with progressive disease early in therapy were excluded from the analysis of the prognostic effect of cumulative drug doses. Survival and disease-free survival were calculated using the method of Kaplan and Meier [19] from diagnosis to January 1994. The chemotherapy dosing characteristics were evaluated for prognostic significance by dividing the patient group around the mean value for a particular characteristic and applying the log-rank test [20]. The multivariate analysis was performed using the Cox [21] proportional hazards regression model on the 25 patients completing therapy. All statistical analyses were performed using StatView 4.01 (Abacus Concepts, Inc., Berkeley, CA).

RESULTS

Patient Characteristics

The median age of the patient group was 13.4 years (range 8.2–17.1). At diagnosis 3 patients had lung metastases and 2 had axial disease. Of the 20 patients who were evaluable for histologic response at the time of delayed primary tumor resection, only 2 had >90% primary tumor necrosis. Five patients had limb salvage operations and 22 had limb amputation. At a median follow-up of 59 months (range 18–154) for surviving patients, 19/27 patients are alive for an overall survival probability of 70%. Nine patients relapsed after achieving first remission at a median of 10 months (range 6–32) from diagnosis, and 2 patients had progressive disease 2 months after beginning chemotherapy, having failed to achieve first remission. Three of the 9 patients with relapsed disease survive free of disease in second remission at 141, 122, and 108 months from relapse. The other 6 patients with relapsed disease and the 2 patients with progressive disease died due to osteosarcoma. The probability of disease-free survival for the group was 59%. There were no deaths in remission.

Relationship Between Chemotherapy Dosing Characteristics and Prognosis

Actual cumulative drug doses were calculated in the 25 patients who completed therapy (Table I) and dichotomized around the mean cumulative dose for HDMTX, ADR, and CDDP. The 2 patients with early progression of disease were excluded from this analysis since their therapy was changed before they completed the intended protocol of HDMTX, ADR, and CDDP. Disease-free survival was calculated for the group of patients above and below the mean, and then was compared using the log-rank statistic. Patients who were given a cumulative HDMTX and ADR dose above the mean had a significantly better disease-free survival (Fig. 1A, B, respectively), while the cumulative CDDP dose administered was not of prognostic value. Both patients with a favor-

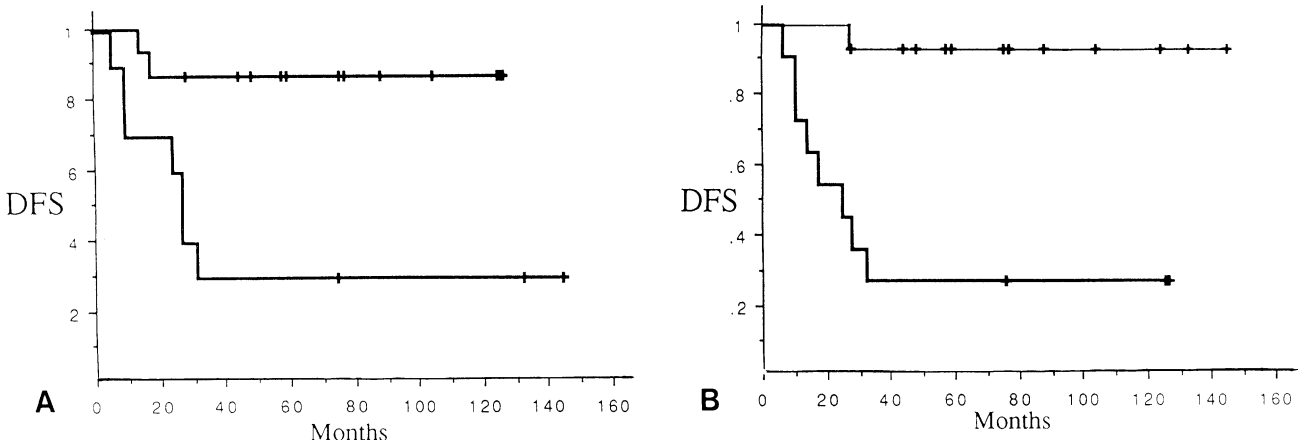

Fig. 1. Probability of remaining disease free (DFS) from time of diagnosis in study patients with OS. **A:** Twenty-five patients subdivided for their cumulative HDMTX dose above and below the mean of 114 g/m^2 ($P = 0.005$). **B:** Twenty-five patients subdivided for their cumulative ADR dose above and below the mean of 303 mg/m^2 ($P = 0.004$). The 2 patients with progressive disease early in therapy were excluded from the cumulative drug dose analyses.

able histologic response received cumulative doses of HDMTX and ADR which were above the mean.

All 27 patients received HDMTX. We postulated that the mean serum MTX values for an individual patient may reflect not only the potential for MTX toxicity, but also the ability of the patient to achieve adequate tumoricidal serum concentrations of the drug and thus predict for survival. We divided the 27 patients into two groups around the mean values for 4 (peak), 24, and 48 hr serum MTX levels (Table II). Only a low mean 48 hr serum MTX level approached prognostic significance ($P = 0.092$).

Using the Cox proportional hazards model we performed a multivariate analysis using the cumulative ADR dose and the cumulative MTX dose. Only higher cumulative ADR ($\chi^2 = 6.302, P = 0.0121$) retained independent, favorable prognostic significance.

One of the 3 patients with pulmonary metastases at diagnosis and 1 of the 2 patients with axial primaries are long-term survivors. In 3 of these 5 patients the cumulative doses of HDMTX and ADR were in the favorable range, or greater than the mean. We did not find a high incidence of unfavorable dosing characteristics in the 5 patients with poor prognostic features (3 with pulmonary metastasis and 2 with axial tumors) at diagnosis.

TABLE II. Serum MTX Levels

Timing of serum sampling	Mean MTX level in μmol/l (S.E.M.)	Disease-free survival	
		χ^2	P
4 hr (peak)	1,002 (72)	1.884	0.167
24 hr	8.38 (1.55)	1.933	0.164
48 hr	0.70 (0.10)	2.833	0.092

DISCUSSION

The value of monitoring serum MTX levels following the administration of HDMTX in OS patients to predict toxicity has long been recognized [22,23]. Moreover, in children with acute lymphoblastic leukemia it has been shown that systemic clearance of intravenous MTX has prognostic significance [24,25]. While a dose-response relationship has been observed in the past for patients with OS receiving HDMTX [26], only recently has the relationship between MTX pharmacokinetics and prognosis been explored [27–29]. Saeter et al. [27] demonstrated that patients with higher 48 hr serum MTX levels had a higher amount of tumor necrosis at delayed primary resection. Peak MTX levels immediately postinfusion were not studied. No details of actual HDMTX doses delivered, or conditions for modifying HDMTX doses for ongoing treatment toxicities, were given. Patients with a higher degree of tumor necrosis had a superior survival rate. In our study, 48 hr serum MTX levels approached significance ($P = 0.09$) as a prognostic factor in the univariate analysis. Our failure to detect a similar finding may be due to the small number of patients with high amounts of tumor necrosis in our study, and to the relatively small overall size of our patient population. It is noteworthy that patients in this Scandinavian study with a poor initial tumor response, and overall survival, received a cumulative dose of HDMTX and ADR well below the mean value in our study, suggesting that cumulative drug dosing may have been prognostically important.

Graf et al. [29] have reported the results of the German Cooperative OS Study (COSS) Group for 3 different protocols using HDMTX throughout the 1980s. They found that the 4 hr peak serum MTX value was predictive of

survival in only 1 protocol (COSS 80). Patients treated with COSS 80 received the highest cumulative HDMTX dose, however, there were several other differences in cumulative dosing, and drugs other than HDMTX, CDDP, and ADR were used in COSS 82 and COSS 86, preventing direct comparisons. A prospective study with consistent cumulative HDMTX doses and, perhaps, tailoring of subsequent HDMTX doses to serum MTX levels will be needed to properly investigate our observations further.

Some doubt exists over the need to administer HDMTX in multiagent chemotherapy protocols for OS. Chemotherapy protocols without HDMTX have achieved excellent survival rates in patients with OS [30]. Furthermore, Bramwell et al. [16] did not demonstrate a benefit for HDMTX when given in addition to CDDP and ADR. However, in this study [16] the cumulative doses of both HDMTX and ADR were low in the 3 drug arm compared to our patient population. Our study is unable to address the role of HDMTX in the therapy of OS patients but instead suggests that a threshold cumulative dose may exist below which prognosis may be adversely affected. The contrary outcome results in various studies utilizing HDMTX may relate to variations in the cumulative dosing characteristics or in the pharmacokinetics of MTX achieved in these patients. Future clinical OS chemotherapy studies should incorporate the dosing characteristics of ADR and HDMTX as prospective variables in the study design.

REFERENCES

1. Link MP, Eilber F: Osteosarcoma. In Pizzo PA, Poaplack DG (eds): "Principles and Practice of Pediatric Oncology." 2nd Ed. Philadelphia: J.B. Lippincott, 1993, pp 841–866.
2. Eilber F, Giuliano A, Eckhardt J, Patterson K, Moseley S, Goodnight J: Adjuvant chemotherapy for osteosarcoma: A randomized prospective trial. J Clin Oncol 5:21–26, 1987.
3. Meyers PA, Heller G, Healey J, Huvos A, Lane J, Marcove R, Applewhite A, Vlamis V, Rosen G: Chemotherapy for non-metastatic osteogenic sarcoma; the Memorial Sloan-Kettering experience. J Clin Oncol 10:5–15, 1992.
4. Jaffe N: Recent advances in the chemotherapy of metastatic osteogenic sarcoma. Cancer 30:1627–1631, 1972.
5. Jaffe N, Farber S, Traggis D, Geiser C, Kim BS, Das L, Frauenberger G, Djerassi I, Cassady JR: Favourable response of metastatic osteogenic sarcoma to pulse high dose methotrexate with citrovorum rescue and radiation therapy. Cancer 31:1367–1373, 1973.
6. Cortes EP, Holland JF, Wang JJ, Sinks LF: Doxorubicin in disseminated osteosarcoma. JAMA 221:1132–1138, 1972.
7. Baum E, Gaynon P, Greenberg L, Krivit W, Hammond D: Phase II study of cisdichlorodiammineplatinum (II) in childhood osteosarcoma: Children's Cancer Study Group report. Cancer Treat Rep 63:1621–1627, 1979.
8. Ettinger LJ, Douglass HO, Higby DJ, Mindell ER, Nime F, Ghoorah J, Freeman AI: Adjuvant adriamycin and cisdiamminedichloroplatinum (cis-platinum) in primary osteosarcoma. Cancer 47:248–254, 1981.
9. Pratt CB, Champion JE, Senzer N, Green AA, Rao B, Douglass E, Meyer WE, Crom DB: Treatment of unresectable or metastatic osteosarcoma with cisplatin or cisplatin-doxorubicin. Cancer 56:1930–1933, 1985.
10. Link MP, Goorin AM, Miser AW, et al.: The effect of adjuvant chemotherapy on relapse-free survival in patients with osteosarcoma of the extremity. N Engl J Med 314:1600–1606, 1986.
11. Hudson M, Jaffe MR, Jaffe N, Ayala A, Raymond K, Carrasco H, Wallace S, Murray J, Robertson R: Pediatric osteosarcoma: Therapeutic strategies, results, and prognostic factors derived from a 10-year experience. J Clin Oncol 8:1988–1997, 1990.
12. Bacci G, Picci P, Riggieri P, et al.: Primary chemotherapy and delayed surgery (neoadjuvant chemotherapy) for osteosarcoma of the extremities. Cancer 65:2539–2553, 1990.
13. Davis AM, Bell RS, Goodwin PJ: Prognostic factors in osteosarcoma: A critical review. J Clin Oncol 12:423–431, 1994.
14. Meyers PA, Heller G, Healey JH, Huvos A, Applewhite A, Sun M, LaQuaglia M: Osteogenic sarcoma with clinically detectable metastasis at initial presentation. J Clin Oncol 11:449–453, 1993.
15. Baldini N, Scotlandi K, Barbanti-Borodano G, et al.: Expression of P-glycoprotein in high-grade osteosarcomas in relation to clinical outcome. N Engl J Med 333:1380–1385.
16. Bramwell VHC, Burgers M, Sneath R, et al.: A comparison of two short intensive adjuvant chemotherapy regimens in operable osteosarcoma of limbs in children and young adults: The first study of the European Osteosarcoma Intergroup. J Clin Oncol 10:1579–1591, 1992.
17. Buice RG, Evans WE, Karas J, Nicholas CA, Sidhu P, Straughn AB, Meyer MC, Crom WR: Evaluation of enzyme immunoassay, radioassay and radioimmunoassay of serum methotrexate as compared with liquid chromatography. Clin Chem 26:1902–1904, 1980.
18. Schroder H, Heinsuig E-M: Enzymatic assay for methotrexate in erythrocytes. Scand J Clin Lab Invest 25:657–659, 1985.
19. Kaplan EL, Meier P: Nonparametric estimation from complete observations. J Am Stat Assoc 53:457–481, 1958.
20. Mantel N: Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 50:163–170, 1966.
21. Cox DR: Regression models and lifetables. J R Stat Soc B 34:187–220, 1972.
22. Jaffe N, Traggis D: Toxicity of high-dose methotrexate (NSC-740) and citrovorum factor (NSC-3590) in osteogenic sarcoma. Cancer Chemother Rep 6:31–36, 1975.
23. Stoller RG, Hande KR, Jacobs SA, Rosenberg SA, Chabner BA: Use of plasma pharmacokinetics to predict and prevent methotrexate toxicity. N Engl J Med 297:630–634, 1977.
24. Evans WE, Crom WR, Stewart CF, Bowman WP, Chen CH, Abromowitch M, Simone JV: Methotrexate systemic clearance influences probability of relapse in children with standard risk acute lymphoblastic leukemia. Lancet 1:359–362, 1984.
25. Borsi JD, Revesz T, Schuler D: Prognostic importance of systemic clearance of methotrexate in childhood acute lymphoblastic leukemia. Cancer Chemother Pharmacol 19:261–264, 1987.
26. Kim J, Djerassi I: Dose-response of osteogenic sarcoma and lung Ca to methotrexate-citrovorum (abstract). Proc Am Assoc Cancer Res 18:123, 1977.
27. Saeter G, Alvegard TA, Elomaa I, Stenwig AE, Holstrom T, Solheim OP: Treatment of osteosarcoma of the extremities with the T-10 protocol, with emphasis on the effects of pre-operative chemotherapy with single-agent high-dose methotrexate: A Scandinavian Sarcoma Group study. J Clin Oncol 9:1766–1775, 1991.
28. Solheim OP, Saeter G, Elomaa I, Alvegard TA: The treatment of osteosarcoma: Present trends. Ann Oncol 3:7–11, 1992.
29. Graf N, Winkler K, Betlemovic M, Fuchs N, Bode U: Methotrexate pharmacokinetics and prognosis in osteosarcoma. J Clin Oncol 12:1443–1451, 1994.
30. Cassano WF, Graham-Pole J, Dickson N: Etoposide, cyclophosphamide, cisplatinum, and doxorubicin as neoadjuvant chemotherapy for osteosarcoma. Cancer 68:1899–1902, 1991.